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Standard Chemotherapy With or Without High-Dose Chemotherapy for Aggressive Non-Hodgkin's Lymphoma: Randomized Phase III EORTC Study

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Background: **The long-term outcome for patients with aggressive non-Hodgkin's lymphoma (NHL) is poor. Consequently, the European Organization for Research and Treatment of Cancer Lymphoma Group designed a prospective randomized trial to investigate whether high-dose chemotherapy plus autologous bone marrow transplantation (ABMT) after standard combination chemotherapy improves long-term survival.** ***Methods:*** **Patients aged 15–65 years with aggressive NHL received three cycles of CHVmP/BV polychemotherapy (i.e., a combination of cyclophosphamide, doxorubicin, teniposide, and prednisone, with bleomycin and vincristine added at mid-cycle). After these three cycles, patients with a complete or partial remission and at that time no lymphoma involvement in the bone marrow were randomly assigned to the ABMT arm (a further three cycles of CHVmP/BV followed by BEAC [i.e., a combination of carmustine, etoposide, cytarabine, and cyclophosphamide] chemotherapy and ABMT) or to the control arm (five more cycles of CHVmP/BV). All statistical tests are two-sided.** ***Results:*** **From December 1990 through October 1998, 311 patients (median age = 44 years) were registered and received the first three cycles of CHVmP/BV, and 194 patients were randomly assigned to the treatment arms. Approximately 70% (140 patients) of these patients were of low or low–intermediate International Prognostic Index (IPI) risk. After a median follow-up of 53 months, an intention-to-treat analysis showed a time to disease progression and overall survival at 5 years of 61% (95% confidence interval [CI] = 51% to 72%) and 68% (95% CI = 57% to 79%), respectively, for the ABMT arm and 56% (95% CI = 45% to 67%) and 77% (95% CI = 67% to 86%), respectively, for the control arm. Differences between arms were not statistically significant. A subset analysis on IPI risk groups, although too small for reliable statistical analysis, yielded similar results.** ***Conclusions:*** **Standard combination therapies remain the best choice for most patients with aggressive NHL. We recommend that patients with IPI low or low–intermediate risk not be subjected to high-dose chemotherapy and ABMT as a first-line therapy. [J Natl Cancer Inst 2001;93:22–30]**

Patients with advanced aggressive non-Hodgkin's lymphoma (NHL) can be treated effectively with multiagent chemotherapy. Although the majority of patients younger than the age of 65 years will reach a complete remission (CR) after CHOP-like chemotherapy (i.e., combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone), fewer than 50% will be finally cured *(1).* More intensive chemotherapy regimens *(2–5)* generally yielded high percentages of CR, up to 80%, but did not improve the disease-free survival when compared with the results with CHOP: In a large randomized trial comparing three intensive chemotherapy regimens with classical CHOP, no difference was found among the four regimens *(6).*

In 1975, the European Organization for Research and Treatment of Cancer (EORTC) designed CHVmP, a polychemotherapy regimen derived from CHOP, consisting of courses of cyclophosphamide, doxorubicin, teniposide, and prednisone repeated every 3 weeks, for patients with NHL. In the second-generation EORTC trial for patients with stage III or IV NHL who were aged up to 70 years, with intermediate- and high-grade malignancy [Working Formulation *(7)*], CHVmP alone was compared with CHVmP to which bleomycin and vincristine were added at mid-cycle (CHVmP/BV). The CHVmP/BV scheme resulted in a higher rate of CR (74% versus 49%) with a better overall survival at 5 years (53% versus 29%) *(8)* and 10 years (34% versus 22%) *(9).* The next EORTC randomized study that compared CHVmP/BV with the third-generation regimen ProMACE-MOPP (i.e., a combination of prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide, followed by mechlorethamine, vincristine, procarbazine, and prednisone) found identical survival between the two arms but with far less toxicity for patients in the CHVmP/BV arm *(10).*

In the mid-1980s, high-dose chemotherapy followed by autologous stem cell rescue became a mature therapy option that had activity for relapsing and refractory NHL *(11–14).* Obviously, dose escalation appeared to cure some patients with conventional chemotherapy-resistant disease. In large overviews covering more than 1200 patients, Goldstone et al. *(15)* and Armitage *(16)* documented that this form of bone marrow ablative therapy resulted in long-term disease-free survival in more than half of the patients who received a transplant at a time of minimal disease early in the course of their lymphoma. However, selection might have played a major role in the outcome of

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See "Notes" following "References."

these patients because none of these patients had been treated in randomized phase III trials.

Therefore, in 1990, with the aim of improving the outcome of patients with aggressive NHL, the EORTC Lymphoma Group designed a prospective randomized study (EORTC 20901) comparing the EORTC gold-standard regimen (eight cycles of CHVmP/BV) with six cycles of CHVmP/BV followed by consolidation BEAC (i.e., a combination of carmustine, etoposide, cytarabine, and cyclophosphamide) high-dose chemotherapy. The bone marrow ablative therapy was given to patients who had reached a minimal residual disease status. Herein, we present the results from the study after a median follow-up of 53 months.

Patients and Methods

Patients

Newly diagnosed patients aged 15–60 years with NHL of stages II–IV were registered. After 1997, the upper age limit was increased to 65 years because of slow accrual and the fact that the transplant procedure was well tolerated in the eldest patients of the cohort. For inclusion, the criteria of the Working Formulation *(7)* for NHL had to be fulfilled and the lymphoma had to be of intermediate-grade histology (categories D, E, F, and G). In addition, patients with stage I bulky NHL or stages II–IV of the following types were acceptable: diffuse large-cell immunoblastic lymphoma, anaplastic large-cell lymphoma, large-cell and small-cell (if containing numerous blasts) pleomorphic T-cell lymphoma, and angioimmunoblastic lymphoma with dysproteinemia-like T-cell lymphoma. Patients with low-grade NHL, lymphoblastic NHL, and Burkitt's lymphoma were excluded. Staging evaluation included a full hematologic and chemical laboratory survey, a chest x-ray, a computerized tomography scan of the thorax and abdomen, a bone marrow biopsy, an ear, nose, and throat consultation, and, if indicated, additional studies, such as endoscopy, bone scan, or cerebrospinal fluid analysis. In addition, a cardiac ejection fraction at rest and pulmonary function studies, including spirometry and carbon monoxide diffusion measurements, were performed. Patients were required to have a World Health Organization (WHO) performance status of 2 or less without severe cardiac, pulmonary, neurologic, or metabolic disease. The patients gave informed consent for both registration and randomization according to the rules of the local center.

Pathology

A diagnosis based on good-quality histology and made by the local pathologist was accepted. Directly after registration, the local pathologist was required to send in six unstained slides for central pathology review. The final classifying diagnosis was based on the central review and was made according to the revised European–American lymphoma (REAL) classification *(17)*.

Study Design and CHVmP/BV Therapy

The study design is shown in Fig. 1. Patients who had achieved a CR or a partial remission (PR) after the first three cycles of CHVmP/BV were randomly assigned to treatment. Each cycle (3-week duration) of CHVmP/BV chemotherapy consisted of cyclophosphamide at a dose of 600 mg/m^2, doxorubicin at 50 mg/m^2, and teniposide at 60 mg/m^2 given intravenously on day 1, with prednisone at 40 mg/m^2 given orally on days 1, 2, 3, 4, and 5. On day 15, bleomycin at 10 mg (in total) and vincristine at 1.4 mg/m^2 (to a maximum of 2 mg) were given intravenously.

The following dose adaptations were advised: Full doses were always given in the first course, irrespective of the initial blood cell counts. Subsequent courses were postponed for 1 week if, at day 1, there were fewer than 3×10^6 leukocytes/mL or fewer than 100×10^6 thrombocytes/mL. If, after 1 week, cytopenia had not recovered, the three intravenously administered drugs were given at 75% ($3–4 \times 10^6$ leukocytes/mL) or 50% ($2–3 \times 10^6$ leukocytes/mL or $50–100 \times 10^6$ platelets/mL). If the counts were lower than these values, only prednisone, vincristine, and bleomycin were given. Bone marrow depression was never a reason to adjust the doses of bleomycin and vincristine. These drugs were adjusted only when pulmonary (bleomycin) or neurologic (vincristine) toxicity was observed.

All patients received three cycles of treatment and were evaluated after the third full course. If patients had a CR or a PR without histologically proven lymphoma involvement in the bone marrow after the third cycle and were without contraindications for bone marrow ablative chemotherapy (WHO performance status of 0 or 1; no problems harvesting bone marrow or no severe cardiac, pulmonary, neurologic, infectious, or metabolic disease), they were randomly assigned to the autologous bone marrow transplantation (ABMT) arm or to the control arm. Patients in the ABMT arm received three more cycles of CHVmP/BV, followed by BEAC chemotherapy and autologous stem cell rescue. Patients in the control arm received five more cycles of CHVmP/BV. Before BEAC chemotherapy, the following eligibility criteria had to be fulfilled: CR or PR, performance status of 0 or 1, no lymphoma infiltration in the bone marrow at the time of stem cell harvest, adequate numbers of frozen stem cells (*see below*), a cardiac ejection fraction of 0.5 or more, a vital capacity of 70% or more of predicted value, a carbon dioxide diffusion capacity of 50% or more, and the absence of other factors compromising the aplasia period. If these criteria were not fulfilled, the patient was treated according to the control arm scheme.

Radiotherapy

For patients who had a PR after standard chemotherapy, radiotherapy was mandatory. All areas with macroscopically residual disease after eight cycles of

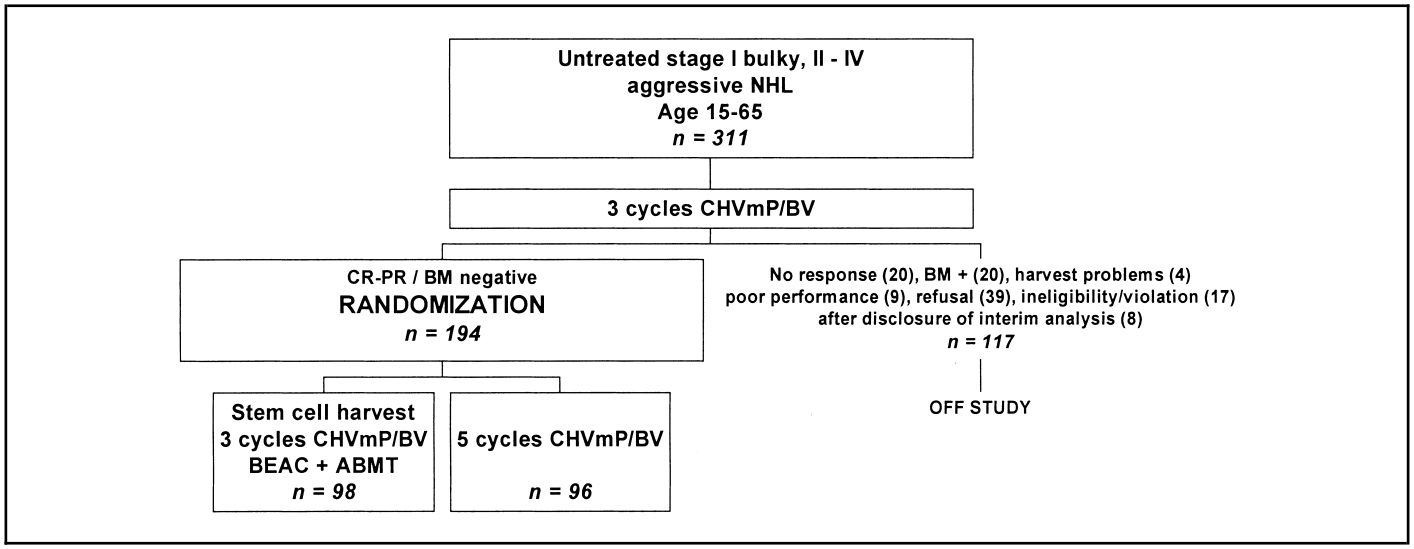

Fig. 1. Outline of the European Organization for Research and Treatment of Cancer 20901 study. NHL = non-Hodgkin's lymphoma; CHVmP/BV = polychemotherapy regimen given every 3 weeks (a combination of cyclophosphamide, doxorubicin, teniposide, and prednisone, with bleomycin and vincristine added at mid-cycle); CR–PR = complete remission–partial remission; BM = bone marrow; BEAC = a combination of carmustine, etoposide, cytarabine, and cyclophosphamide. BM + = positive, i.e., with lymphoma involvement.

CHVmP/BV were irradiated (30-Gy total dose on the whole area, followed by a 10-Gy boost on the residual disease site). Radiotherapy started within 3–4 weeks after the end of the last chemotherapy.

For patients in the control arm who had a CR at the end of chemotherapy, additional iceberg radiotherapy according to EORTC usage was advised (but was not mandatory). Iceberg radiotherapy is defined as radiotherapy (30 Gy) for all areas with disease with an initial diameter greater than 5 cm and for areas with macroscopically residual disease after three cycles of CHVmP/BV. Radiotherapy after ABMT was left to the discretion of the physician but was advised for those patients with bulky mediastinal lymphomas. Iceberg radiotherapy started within 3–4 weeks after the end of chemotherapy.

Autologous Stem Cell Transplantation and BEAC Therapy

Stem cells were harvested after patients were randomly assigned to treatment, preferably between the fourth and sixth cycles of CHVmP/BV. In most patients, a total of 2–3 $\times$ 10^8 bone marrow cells per kilogram of body weight were harvested. During the later years of the study, stem cell harvesting from peripheral blood was permitted, but only if granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor given after the CHVmP/BV chemotherapy was used as a sole factor to induce stem cell mobilization. Additional chemotherapy was not permitted to facilitate stem cell mobilization. ABMT had to be performed within 6 weeks after the last chemotherapy course. As pretransplant measures, the protocol advised the use of a central venous catheter, parenteral nutrition when oral energy intake became insufficient, partial antibiotic (scheme according to the rules of the local center) decontamination of the digestive tract, and a stay in a laminar air flow room. Decontamination procedures started approximately 1 week before the BEAC regimen was initiated. Decontamination was discontinued according to the rules of the local center but not before the patient had a minimum of 0.5 $\times$ 10^6 granulocytes/mL, measured on 2 consecutive days. Hematologic supportive care involved prophylactic leukocyte-poor (filtered) platelet transfusions at least when there were fewer than 10 $\times$ 10^6 platelets/mL as well as therapeutic transfusions when clinically indicated. Filtrated packed red blood cells were used to maintain a hemoglobin concentration greater than 10 g/dL. All blood products were irradiated (15 Gy).

BEAC chemotherapy *(18)* consisted of carmustine at a dose of 300 mg/m^2 given intravenously on day 1; etoposide at a dose of 200 mg/m^2 given intravenously on days 2, 3, 4, and 5; cytarabine at a dose of 200 mg/m^2 given intravenously on days 2, 3, 4, and 5; and cyclophosphamide at a dose of 35 mg/kg given intravenously on days 2, 3, 4, and 5 with detoxification using mesna (sodium 2-mercaptoethane sulfonate) at 20 mg/kg (given 10 minutes before and 4, 8, 12, and 16 hours after cyclophosphamide). After a 1-day rest (day 6), stem cells were reinfused on day 7.

Registration and Randomization

All patients were registered and randomly assigned at the EORTC Data Center by Internet (EUROCODE program) or by telephone. Patients were randomly assigned by use of the minimization technique with the institution number as the only factor for stratification, which resulted in 50% of the assignments being deterministic. Because there were no known prognostic factors at the time of protocol development, no other factor was used. At registration and at randomization, the inclusion/exclusion criteria were verified and had to be fulfilled before any patient was accepted. All patients had to be registered before the start of chemotherapy.

Data Management

Double entry of all data, collected on case report forms, was performed. Cross-checks for missing forms and inconsistent data were done throughout the study according to standard operating procedures of the EORTC Data Center. Twice a year, the study coordinator (H. C. Kluin-Nelemans) evaluated the patients' files at the Data Center.

Response Evaluation

The disease in all patients was restaged after three cycles, after six cycles (ABMT arm), or after eight cycles (control arm) of CHVmP/BV and after completion of the final treatment (BEAC and/or radiotherapy). All initially involved sites had to be measured and documented. The response to treatment was assessed according to the WHO criteria *(19)*.

End Points and Statistical Considerations

Time to disease progression and overall survival were the end points used. Time to disease progression is the time between the date of randomization to the date of disease progression. If progression was not observed, the patient was censored at the date of the last examination. Overall survival is the time between the date of randomization and the date of death from any cause. Patients who were still alive when last contacted were censored at the date of last follow-up. For the patients who were not randomly assigned, the overall survival was calculated as the time between the date of registration and the date of death. One hundred assessable patients were to be randomly assigned to each therapeutic arm, which would ensure enough relapses 5 years after the last randomization to detect a difference of 20% (from 50% to 70%) in the median time to disease progression ($\alpha = 0.05$; $\beta = 0.2$). We assumed that 66% of the registered patients were eligible and randomly assigned, necessitating 300 patients for registration. All analyses of the randomly assigned patients were done on an intention-to-treat basis. Survival curves were estimated by use of the Kaplan–Meier method *(20)* and compared by use of the log-rank test *(21,22)*. All statistical tests used were two-sided.

Interim Analysis

The protocol did not foresee an interim analysis or an Independent Data Monitoring Committee. However, because of a decrease in the accrual from 1995 onward, the EORTC Protocol Review Committee permitted an interim analysis. This analysis was performed in October 1998, with the software package EaST (CYTEL Software Corporation) to test whether there was sufficient evidence for (or against) the effectiveness of the ABMT treatment and to determine whether the study should be continued. The O'Brien–Fleming stopping rule *(23)* was applied, and the log-rank test *(24,25)* was performed. At that time, 307 patients had been registered and 181 patients had been randomly assigned. The aim was to detect a hazard ratio of 0.515 with a power of 80% and a nominal statistical significance level of 5% (two-sided test) in the time to progression. The analysis was performed by the EORTC Data Center and discussed by an Independent Data Monitoring Committee, consisting of non-EORTC members. After the group committed to follow the advice of the Independent Data Monitoring Committee, the results were disclosed on October 17, 1998.

RESULTS

Interim Analysis Results

The O'Brien–Fleming stopping rule for boundaries following an alpha spending function approach *(23)* was applied as appropriate for cancer clinical trials. At the time of the interim analysis, 56 of the 80 events required had occurred, and the critical value of the test statistic was 0.813 [$(O - E)/(V)^{1/2}$, where $Z \sim N(0,1)$, O is the observed number, E is the expected number, V is the variance, Z is a random variable that is distributed as a standardized normal distribution with a mean of 1 and a variance of 1, and N is the normal distribution]. With the use of a shape parameter of 0.0 and given the previous number of events, the boundary values of 2.29 to reject the null hypothesis (H_0) and 1.33 to reject the alternative hypothesis (H_1) were calculated. Because the critical value of the test statistic was smaller than the value to reject H_1 (0.813 < 1.33), the Independent Data Monitoring Committee advised that the study be stopped owing to evidence of a lack of effectiveness of the ABMT treatment over the control therapy. Patients who had been registered shortly before October 1998 were not allowed to undergo the randomization procedure; instead, they received the control arm therapy.

Final Analysis Results

This analysis used a median follow-up of 53 months (range = 47–58 months) for randomly assigned patients. Data entry

was closed on December 31, 1999. From December 1990 through October 1998, 311 patients were registered (Table 1). The classification of pathology, initially based on the Working Formulation *(7),* was reclassified according to the REAL classification *(17)* and is shown in Table 2. On the basis of a central review of the pathology, 18 patients (12 with follicular lymphoma and six with Burkitt's lymphoma) were considered to be ineligible. Nevertheless, all patients were analyzed on the basis of the intention-to-treat principle.

Protocol Adherence

Patients could be randomly assigned only if they had responded after three cycles and had no lymphoma involvement in the bone marrow. Transplantation after the sixth cycle could be performed only in the absence of contraindications for bone marrow ablative chemotherapy (i.e., patients whose disease relapsed or progressed during cycles 4–6 or who developed toxic effects or other conditions compromising the aplasia period were not allowed to undergo the high-dose chemotherapy). The latter group received—according to the protocol—the complete eight cycles of treatment given to the control arm. The protocol adherence is summarized in Table 3. A total of 194 patients were randomly assigned: 98 patients to the ABMT arm and 96 patients to the control arm. The clinical characteristics, including the International Prognostic Index (IPI) risk profile, and pathology subgroups were well balanced between the arms. Approximately 70% (140 patients) belonged to the low- or low–intermediate-IPI-risk category (Tables 1 and 2). The reasons why 117 patients were not randomly assigned are given in Table 3. Of these patients, 86 received the chemotherapy according to the control arm, five received high-dose chemotherapy followed by stem cell transplantation, eight received other chemotherapy, two received radiotherapy, and two were not treated at all. We had no information from 14 patients.

Of 98 patients randomly assigned to undergo the high-dose chemotherapy, 61% were treated accordingly. Thirteen of these 98 patients belonged to the IPI high–intermediate-risk group and two belonged to the IPI high-risk group. Two more were conditioned by BEAM (BEAC except that cyclophosphamide is replaced with melphalan) instead of BEAC. The reasons why 38 patients did not undergo the transplant procedure are given in Table 3. Apart from those patients who had a relapse while on CHVmP/BV, most other patients in the ABMT arm who did not get BEAC were treated according to the protocol by the control arm and received five more cycles of CHVmP/BV instead. Only two patients randomly assigned to the control arm received autologous stem cell transplantation as consolidation therapy.

Table 1. European Organization for Research and Treatment of Cancer 20901 study: characteristics of all patients at registration*

Characteristic	ABMT arm (n = 98)	Control arm (n = 96)	Patients not randomly assigned (n = 117)	All patients (n = 311)
Median age, y (range)	41 (16–65)	44 (16–63)	48 (20–65)	44 (16–65)
% male	60	63	62	62
% stage I	6	10	3	6
% stage II	37	38	24	32
% stage III	24	24	17	22
% stage IV	33	28	56	40
% B symptoms†	36	37	35	36
% positive bone marrow	15	11	30	19
% with ⩾2 extranodal sites	10	9	18	13
% elevated LDH	47	50	51	49
% bulky disease >10 cm	46	42	48	46
% patients ⩽60 y old	97	98	97	97
% age-adjusted IPI				
Low risk	26	24	15	21
Low–intermediate risk	43	47	41	43
Intermediate–high risk	26	22	33	28
High risk	5	7	11	8

*ABMT = autologous bone marrow transplantation; IPI = International Prognostic Index; LDH = lactate dehydrogenase.

†Ann Arbor classification system *(42).*

Radiotherapy

Of 37 patients in PR after eight cycles of CHVmP/BV, 31 received radiotherapy (22 patients from the control arm, five patients from the ABMT arm, and four patients in the group that had not been randomly assigned to treatment). The disease status of 10 patients (32%) subsequently converted from PR to CR. Iceberg radiotherapy was optional according to the protocol and was given to 81 patients, 25 of 98 patients in the ABMT arm and 56 of 96 patients in the control arm.

Table 2. Pathology after central review according to the Revised European–American lymphoma classification *(17)**

Pathology	ABMT arm (n = 98), No. (%)	Control arm (n = 96), No. (%)	Patients not randomly assigned (n = 117), No. (%)	All patients (n = 311), No. (%)
Diffuse large B-cell lymphoma	49 (50)	56 (58)	55 (47)	160 (51)
Primary mediastinal large B-cell lymphoma	2 (2)	2 (2)	1 (1)	5 (2)
Mantle cell lymphoma	1 (1)	3 (3)	9 (8)	13 (4)
Marginal zone B-cell lymphoma	2 (2)	3 (3)	4 (3)	9 (3)
Anaplastic large-cell lymphoma	18 (18)	11 (11)	9 (8)	38 (12)
Peripheral T and AILD-like T-cell lymphoma	1 (1)	2 (2)	5 (4)	8 (3)
Other	2 (2)	3 (3)	5 (4)	10 (3)
Unclassifiable†	19 (19)	11 (11)	20 (17)	50 (16)
Ineligible: follicular lymphoma‡	4 (4)	2 (2)	6 (5)	12 (4)
Ineligible: Burkitt's lymphoma‡		3 (3)	3 (3)	6 (2)

*AILD-like = angioimmunoblastic lymphoma with dysproteinemia; ABMT = autologous bone marrow transplantation.

†Patients were considered unclassifiable if material for central review was not available or considered to be of insufficient quality.

‡Patients were registered upon the non-Hodgkin's lymphoma classification made by the local pathologist. This might explain the inclusion of these 18 ineligible patients. In spite of ineligibility, all patients were used in the analysis.

Table 3. Protocol adherence*

No. of patients registered (%)	311 (100)
No. of patients off protocol between registration and randomization (%)	117 (38)
No change or disease progression after three cycles of CHVmP/BV	20 (17)
Positive bone marrow after three cycles of CHVmP/BV	20 (17)
No hematopoietic colony growth or other harvest problems	4 (3)
Poor performance status or concurrent disease	9 (8)
Refusal for randomization	39 (33)
Ineligibility/protocol violation/missing data	13 (11)
Administrative complications	4 (3)
After disclosure of interim analysis	8 (7)
No. of patients randomly assigned to treatment (%)	194 (62)

	ABMT arm (n = 98)	Control arm (n = 96)	Total (n = 194)
Fulfilled protocol	60 (61)	82 (85)	142 (73)
Did not fulfill protocol	38 (39)	14 (15)	52 (27)
Relapse/progression during cycles 4–6 of CHVmP/BV	12 (32)	9 (64)	21 (40)
Excessive toxicity	6 (16)	1 (7)	7 (13)
Refusal after randomization	15 (39)		15 (29)
Protocol violation		2 (14)	2 (4)
Lost to follow-up/no data	5 (13)	2 (14)	7 (13)

*CHVmP/BV = polychemotherapy regimen, given every 3 weeks (i.e., cyclophosphamide, doxorubicin, teniposide, and prednisone, with bleomycin and vincristine added at mid-cycle); ABMT = autologous bone marrow transplantation.

Toxicity of the CHVmP/BV Regimen

All dose adjustments of the CHVmP/BV regimen were recorded. Of the 1634 CHVmP/BV cycles given, 74% were followed by hematologic toxicity. The main toxicity concerned grade 3 or 4 granulocytopenia, which was observed in 74%–85% of the cycles throughout the whole treatment period. Grade 3 or 4 thrombocytopenia varied from 24% to 28%, and grade 3 or 4 anemia varied from 27% to 34%. Except for alopecia, nonhematologic toxicity was rare with 4% at WHO grade 3 level. Two patients developed a WHO grade 4 infection, and one patient had a grade 4 hemorrhage. The deaths of two patients were related to the CHVmP/BV treatment: One patient with stomach involvement died after the first course as a result of stomach perforation and bleeding, and the other patient died despite a liver transplantation after exacerbation of a hepatitis B viral infection. CHVmP/BV chemotherapy was given on time and at a full dose in 80% of the cycles. In 15% of the cycles, a delay of more than 1 week occurred for the combination of cyclophosphamide, doxorubicin, teniposide, and prednisone; a similar delay occurred in 10% of the bleomycin and vincristine treatments. Dose reductions occurred in 6% of cyclophosphamide, doxorubicin, and teniposide treatments; in 1% of prednisone treatments; in 5% of bleomycin treatments; and in 9% of vincristine treatments. In the ABMT arm, 31% of cycles 4–6 were postponed compared with 18% in the control arm, probably to enable stem cell harvesting during that period.

ABMT, Aplasia Period, and BEAC Toxicity

Of the 60 patients given an ABMT, 47 were given bone marrow-derived stem cells and the remaining 13 patients were given peripheral blood-derived stem cells. A median number of 2.25×10^8 nucleated cells per kilogram was reinfused. The median number of days in the hospital, including the 7-day period of BEAC chemotherapy, was 25.5 days (range = 11–47 days). The median number of days that patients had a granulocyte count of fewer than 0.5×10^6 cells/mL was 10 days (range = 1–25 days); for a granulocyte count of fewer than 0.1×10^6 cells/mL, it was 8 days (range = 2–19 days). The median number of days with fever higher than 38 °C was 4 days (range = 0–20 days). The median number of platelet transfusions was three (range = 0–29 transfusions). No death was caused by toxicity. One grade 4 nonhematologic toxicity was caused by septicemia. Fifteen patients developed some grade 3 toxicity (i.e., six had an infection, four had diarrhea, four had mucositis, and one had pulmonary complications).

Final Analysis Responses and Prognostic Factors

The responses evaluated at the end of therapy are presented in Table 4. Given the strong predictive effect of the IPI risk factors *(26),* survival curves were also related to these categories. Because 97% of the patients were younger than 60 years, the age-adjusted IPI *(26)* was used; a clear delineation of these risk groups was seen (Fig. 2). Data for the randomly assigned patients are shown in Fig. 3. If all 311 patients were taken into account, the curve for the patients who were not randomly assigned to treatment was below the curve for those who were (data not shown). Of the 98 patients in the ABMT arm, 61% (95% confidence interval [CI] = 51% to 72%) were free from disease progression and 68% (95% CI = 57% to 79%) were alive at 5 years. For the 96 patients in the control arm, 56% (95% CI = 45% to 67%) were free from progression and 77% (95% CI = 67% to 86%) were alive at 5 years. Curves showed no statistically significant difference. A subset analysis on the IPI risk groups yielded similar results when the low-risk and low–intermediate-risk groups were pooled and the intermediate–high-risk and high-risk groups were pooled (Fig. 4). Although the numbers were too low for statistical analysis, there was no suggestion favoring ABMT in any risk group. Thus far, 46 patients have died, 26 in the ABMT arm and 20 in the control arm. Table 5 presents the causes of death.

Discussion

This EORTC study shows that high-dose chemotherapy after standard chemotherapy does not improve the time to disease progression and the overall survival of patients with aggressive NHL. The results of this study are in line with those of several other multicenter randomized studies that incorporated bone marrow ablative chemotherapy for this category of patients *(27–34).* However, the EORTC 20901 study essentially differs from most other studies, which are discussed below.

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) LNH87 protocol *(27)* studied 464 patients, comparing high-dose chemotherapy followed by ABMT with an intensive sequential

Table 4. Responses to treatment, evaluated at the end of protocol therapy

Response	ABMT* arm (n = 98)	Control arm (n = 96)
% complete remission	69	58
% partial remission	19	30
% no change	0	1
% progressive disease	11	10
% early death	0	0
% missing	1	1

*ABMT = autologous bone marrow transplantation.

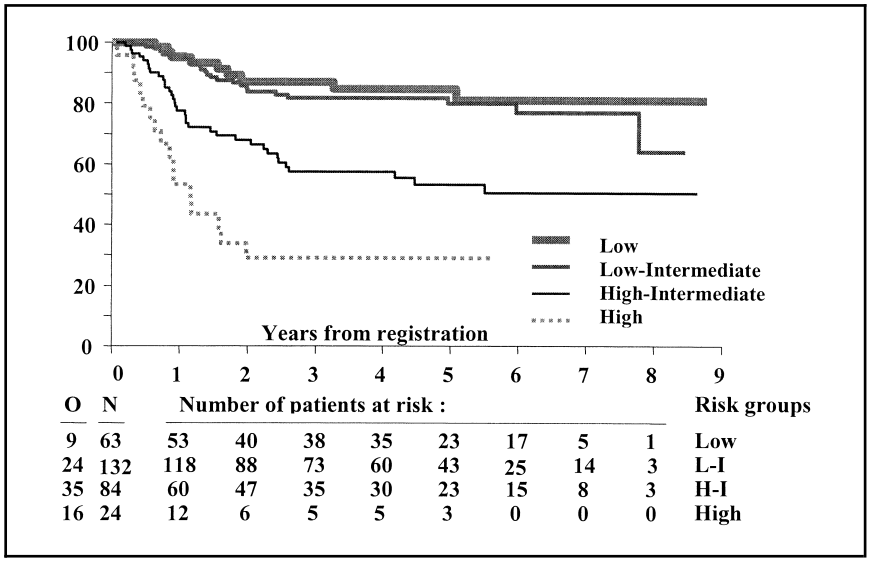

Fig. 2. Kaplan–Meier overall survival curves for all patients (randomly assigned and not randomly assigned) according to age-adjusted International Prognostic Index risk factors. O = observed events; N = number of patients; L-I = low–intermediate; H-I = high–intermediate.

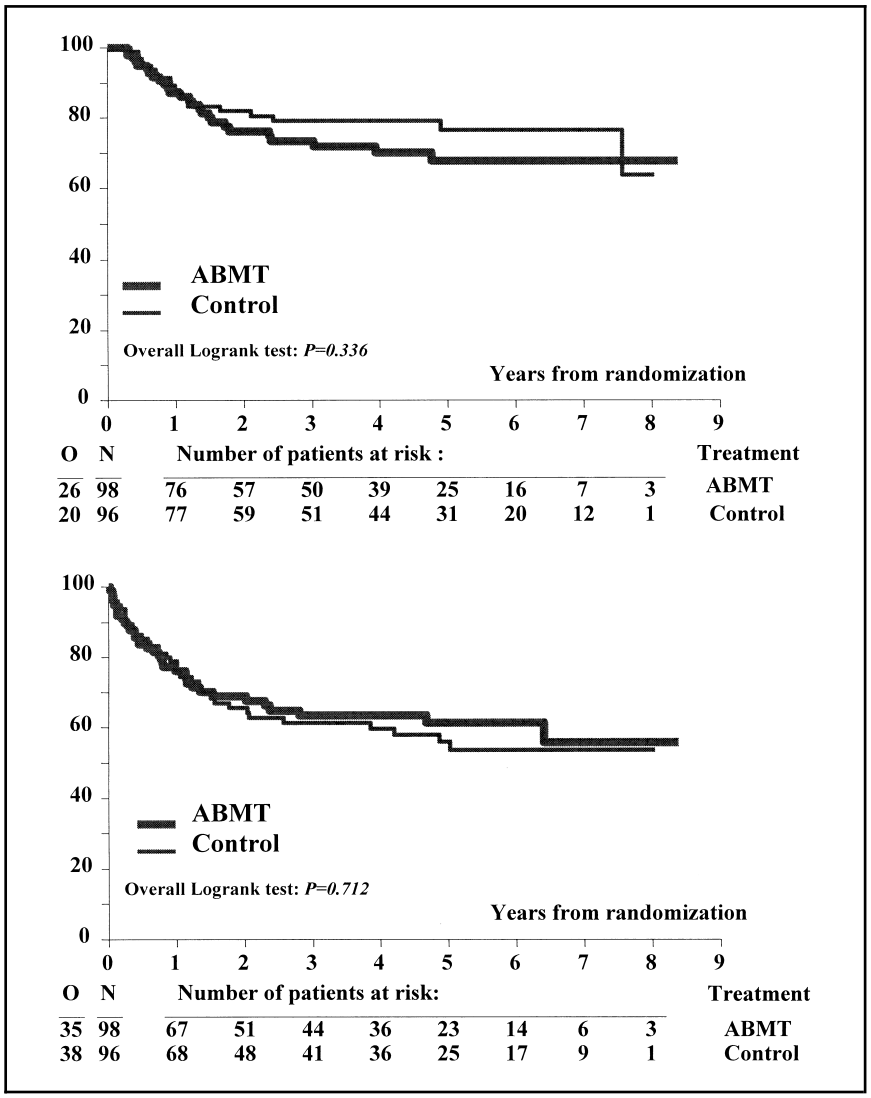

Fig. 3. Kaplan–Meier curves for patients treated according to randomization. Data from all randomly assigned patients are given on the basis of the intention-to-treat analysis. **Upper panel:** overall survival. **Lower panel:** time to disease progression. ABMT = autologous bone marrow transplantation; O = observed events; N = number of patients. All statistical tests are two-sided.

chemotherapy regimen, and found no difference in CR if all patients were taken into account. Updated results showed that ABMT might have been favorable for IPI intermediate–high-risk and high-risk patients *(34)*. However, the next GELA trial (i.e., LNH93–3) *(30)* designed for these poor-risk patients (high-dose chemotherapy after a shortened and intensified induction phase) was prematurely closed because of primary failures and many early relapses.

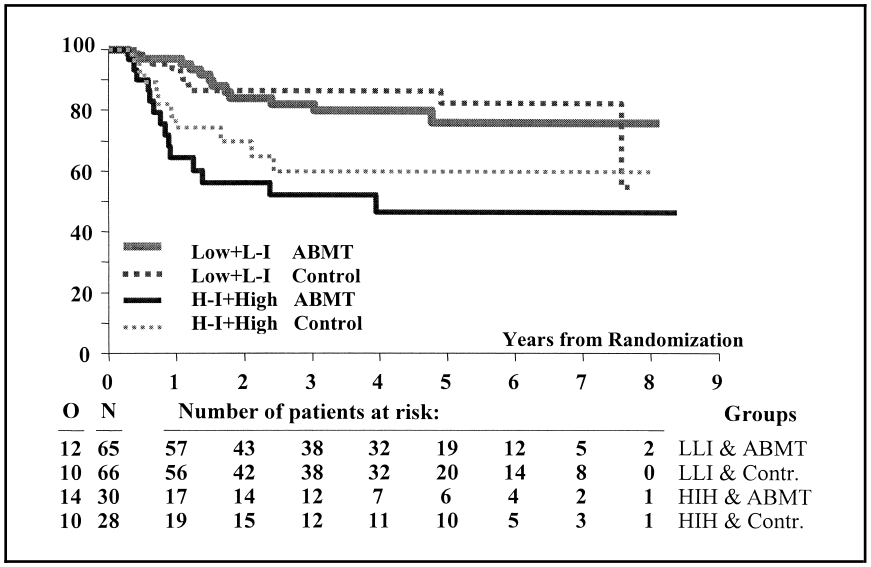

Fig. 4. Kaplan–Meier curves for patients treated according to randomization arm, grouped according to the age-adjusted International Prognostic Index (IPI) risk factors. Data from all randomly assigned patients are given on the basis of the intention-to-treat analysis. ABMT = autologous bone marrow transplantation; O = observed events; N = number of patients; L, low IPI risk; I = intermediate IPI risk; H = high IPI risk.

Table 5. Causes of death

	ABMT* arm (n = 26), No. (%)	Control arm (n = 20), No. (%)
Non-Hodgkin's lymphoma	22 (85)	17 (85)
Infection		1 (5)
Hemorrhage		1 (5)
Other†	3 (12)	
Unknown	1 (4)	1 (5)

*ABMT = autologous bone marrow transplantation.

†One from respiratory insufficiency, one from a cardiovascular event, and one from a car accident.

In the Dutch Organization for Hemato-oncology in Adults (HOVON) 3 study *(28),* ABMT was offered only to patients in PR after three cycles of CHOP and was given directly after the fourth cycle. Sixty-nine patients were randomly assigned to treatment arms, and the calculated difference of 35% between both arms was not reached. Three other randomized trials *(32,33,36),* all offering high-dose chemotherapy and ABMT after only a short induction phase, yielded similar negative results.

Gianni et al. *(29)* studied 98 randomly assigned patients given either a very toxic sequential high-dose chemotherapy regimen plus ABMT or MACOP-B (a combination of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) chemotherapy. At 7 years, the ABMT arm had higher time to disease progression and event-free survival and showed a trend toward improvement in overall survival *(29).* Finally, the Italian NHL Cooperative Study Group *(31)* treated 124 patients with a 12-week VACOP-B (i.e., a combination of etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) regimen or with DHAP (i.e., a combination of dexamethasone, high-dose cytarabine, and cisplatin) salvage with high-dose chemotherapy and ABMT. No difference in favor of the more intensive arm was observed. However, a subset analysis of patients with unfavorable IPI scores suggested a benefit for the ABMT-based therapy, which was restricted to disease-free survival only.

In contrast to these studies, the EORTC 20901 trial treated all patients first with a nearly full-term classical CHOP-like therapy. As consolidation, patients in CR or PR received additional high-dose chemotherapy. To avoid imbalance in duration between both arms, we compared the usual eight cycles of CHVmP/BV with six cycles of CHVmP/BV followed by BEAC and ABMT. The late randomization procedure (i.e., after cycle 3) increased the percentage of patients who could not be randomly assigned or who refused to be randomly assigned, despite informed consent at the start of therapy. Early randomization at registration might have avoided this problem, but it would have introduced a risk of imbalance later. Similarly, because the actual transplant took place after cycle 6, or 3 months after randomization, a considerable number of patients developed conditions (progressive disease or toxic effects) for which BEAC therapy was considered to be useless or too toxic.

Importantly, the majority of the EORTC patients belonged to the favorable IPI risk category *(26).* In a subset analysis of patients in the IPI unfavorable risk categories, no differences were seen between treatment arms. A regression survival model would have been informative for the different risk groups, but the small numbers of the groups in the current study did not allow us to perform such an analysis. This analysis could be done in future clinical trials.

At the time that the EORTC 20901 protocol was written, a 20% difference in time to disease progression at 5 years in favor of the ABMT therapy was expected. The Dutch HOVON 3 study *(28)* was even more optimistic and was estimated to detect a 35% difference in 2-year event-free survival. Gianni et al. *(29)* aimed at a 25% difference, Santini et al. *(31)* aimed at a 20% difference, and the GELA study *(27)* aimed at a 15% difference in disease-free survival at 2 years but compared the ABMT with intensive consolidation chemotherapy. The EORTC study was powered to detect this 20% difference because we assumed that any smaller difference would not be clinically relevant in view of the expected toxicity of the ABMT arm. A 20% difference would nowadays be considered to be too optimistic. Moreover, given the low BEAC-related short-term toxicity, smaller differences would be of interest too. Presently, we are unaware of any long-term toxicity associated with the BEAC regimen. However, alarming new data demonstrate a high incidence of secondary malignancies after ABMT procedures *(37–41).* These data question the merit of submitting NHL patients to

high-dose chemotherapy if the chances of improvement are not substantial.

In conclusion, the data from this randomized trial support the use of a CHOP-like regimen for most patients with aggressive NHL. Patients with IPI low risk or low–intermediate risk should not be submitted to bone marrow ablative intensification as initial therapy. Because three randomized studies *(27,29,31)* found that high-dose consolidation might be beneficial for high-risk patients and because the outcome for these patients is still disappointing, new studies investigating intensification, but only after a full series of six to eight cycles of standard CHOP-like treatments, need to be done. Only large intergroup randomized studies will be statistically powerful enough to give meaningful answers for the future.

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NOTES

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